REMARKS

This amendment is submitted in an earnest effort to bring this application to issue without delay.

Applicants have retained claims 1 through 10 and are adding new claim 11. Antecedent basis for new claim 11 may be found in the specification on page 4, line 9 to the bottom and in Example 1 on page 5. Thus claims 1 through 11 are now in this application and are now presented for examination.

The Examiner has dropped the original rejection of the claims as obvious in view of the cited prior art as previously applied. However, the Examiner has performed a new prior art search and has given the Applicants a rejection of all claims as obvious in view of the combination of four newly cited and applied prior art references. The central reference in the combination is WO 03/043,641 to USLU which was cited in the International Search Report prepared by the European Patent Office in PCT/TR2004/000024, which corresponds to the instant US national Application. WO 03/043,641 discloses pharmaceutical compositions that contain a mixture of alendronate and sodium alginate for preventing bone loss

although the reference does not disclose coating the alendronate with a polymer such as Eudragit E 100. The Examiner, however, is relaying on the newly cited, published US Patent Application 2002/0150624 to WATANABE et al for its disclosure of coating the alendronate with Eudragit E 100 and is relying on US Patent Application 2001/0051636A1 to BLACK et al and US Patent 6,242,002 to TRITTHART et al for its disclosure of preparing alendronate compositions in the form of a sachet with a sweetener.

The Examiner concludes that it would have been obvious from the combination of these references to make a sachet formulation containing alendronate microparticles coated with a polymer insoluble at a pH of 6 to 7.5, such as Eudragit E 100, and to further include alginic acid or sodium alginate with a sweetener to arrive at the present invention.

Applicants ask that the Examiner reconsider his rejection of the claims in view of this combination of prior art references.

The Examiner believes that USLU *et al.* is the closest prior art because it discloses an orally administered alendronate mixed with alginates as a powder in granule or microparticle form. (See e.g. p. 6, lines 1-8: instant claims 1 and 10). But, at page 6 lines 1-8 USLU does not refer to alendronate in particular, but the group name which is biphosphonates. Also, when looking at the whole document, it is seen that, alendronate is not selected specifically although it had been mentioned in the biphosphonates

group. No specific example containing alendronate is given in the whole document. Therefore, Applicants think that this makes a difference. And also at this specified paragraph, (See e.g., p. 6, lines 1-8), oral administration of the formulation is not highlighted except it is mentioned that the composition may be made into a tablet or capsule. And again when the reference is considered as a whole, it will be apparent that the preferred formulation is a double-layer tablet formulation. See page 4, lines 19 and 20 of the reference. And the sentence on page 6, lines 6 to 8 reads as follows: "They have been granular with use of the above-mentioned binders or powder and milled with filling agents, disintegrants, lubricants and glidants and pressed in tablet or filled in capsules." So, Applicants' instantly claimed compositions containing the alendronate in microparticle form and which is filled into sachet formulation is neither disclosed nor suggested in USLU . The reference does not disclose microparticles of alendronate with or without alginic acid or sodium alginate. And Applicants do not use binders, filling agents, disintegrants or glidants which are listed in USLU , which Applicants also believe makes a big difference. Once again, it is important to note that the invention disclosed and claimed in USLU is directed to a double-layer tablet formulation containing any biphosphonate and alginate and most importantly that the biphosphonate is uncoated and in granule or powder form. Applicants' presently claimed

compositions are directed to alendronate in the form of microparticles that are coated with a polymer soluble at a gastric pH of 1 to 4 and insoluble at the salivary pH of 6 to 7.5. Therefore, the USLU reference is not at all suggestive of the presently claimed invention.

The Examiner also states that USLU discloses that the alginic acid is used in amounts sufficient to prevent esophageal reflux and refers to p. 2, lines 22-27 of the reference. Applicants point out that the phrase "Alginic acid and its salts are used for treatment and prevention of esophageal reflux" which we understand that alginic acids are known to treat and prevent esophageal reflux because this paragragh is at the background part of the invention. This passage refers only to the prior art and does not at all indicate or suggest any advantage to using alginic acid or sodium alginate together with alendronate. And no explanation of what is the "sufficient" amount is disclosed since the reference gives only a "broadcast" range of 1 mg to 2000 mg for the alginate.

The Examiner emphasizes that alendronate sodium is disclosed on p. 2, lines 18-20 of USLU The reference also discloses alendronate for preventing the loss of calcium in bones in amounts ranging from 5-40 mg/day or 35-70 mg/week on p. 3, lines 8-15. But these are references only to the prior art and there is no indication of how much alendronate has been used in the

compositions disclosed in USLU, either in the description of the invention in the specification or in the claims. The only specific disclosure of the amount of alendronate in the compositions is mentioned is where the recommended doses for Fosamax® are mentioned which again is background information. (See p. 3, lines 12-15). The recommended doses for alendronate are not claimed in any independent claim of the Applicants' instant invention.

The Examiner states that the ratio of alginates to alendronate in USLU . reads on the percents of alendronate and alginates in the instant claims, i.e. a 1:1 to 2:3 ratios. Applicants believe that the ratio is mis-stated since the alendronate/alginate ratio comes to a 1:1 to 3:2 ratio. Also, when USLU is analyzed closely, Applicants note that the numerical range for the microcrystalline cellulose to alginate ratio and the numerical range for the microcrystalline cellulose to biphosphonate ratio are defined as 10% to 200% (see p. 5, lines 3-4) and 10% to 1000% (see p. 5, lines 23-24) consequently. Although USLU . does not aim to define the biphosphonate/alginate ratio, a simple calculation leads to a percentage range of 1:5 to 1:1. Contrary to these percentages, the instant claims now presented include a weight percentage of alendronate to total weight as 0.001% - 3% (claim 7) and alginate to total weight as 0.001% - 2% (Claim 9) which leads to an alendronate to alginate ratio of 1:1 to 3:2. It is important to emphasize that Applicants' definition of "therapeutically effective

amount of alginate" is different from that of USLU. Therefore, the presently claimed invention is unique and inventive with the specified percentages of ingredients.

Also, the Applicants' way of formulating the coated alendronate / alginate (alginic acid) mixture as presently claimed is new and inventive as well as the percentages of the ingredients. Applicants emphasize that the reason for preparing the presently claimed compositions as a sachet formulation is that preparing sachet formulations with coated microparticles of alendronate is more feasible and safer in the sense that in the absence of the sachet for protecting and stabilizing the alendronate microparticles coated with the polymer, damage to and destruction of the coated microparticles is highly possible. Therefore the presently claimed invention is unique as a whole with the percentages, the coating and the of formulation in a sachet. When one considers the USLU reference, which is identified by the Examiner as the closest prior art, it is clearly seen that the compositions disclosed in the reference are far removed from those of the presently claimed invention.

The secondary prior art references that the Examiner mentions in the office action include WATANABE *et al.* This reference discloses a pharmaceutical composition for oral use with improved absorption which comprises a drug, aminoalkyl methacrylate copolymer E and an acidic substance. This reference provides one

"skilled in the art" with no motivation to coat alendronate with EUDRAGIT E100 in order to prevent esophageal irritation since WATANABE *et al.* use the coating for increasing the absorptivity of alendronate in the digestive tract after the patient eats a meal. See paragraphs [0005] and [0028] through [0030] of the reference. It is also mentioned in WATANABE *et al.* that aminoalkyl methacrylate copolymer E is used in order to mask the bitter taste and the color of drugs, to provide moisture resistance and to increase solubility of slightly soluble drugs (see paragraphs [0016] and [0017]) of the reference, which again are not the purposes of the Applicants' presently claimed invention for using this alginate coating agent. Thus there is no motivation for one "skilled in the art" to combine the teachings of WATANABE et al to coat alendronate with a polymer to improve the patient's absorption of the alendronate and to mask the taste and appearance of the alendronate which has no connection at all with the teachings of USLU to employ alginic acid or sodium alginate together with alendronate for the purpose of preventing gastroesophageal reflux. Furthermore combining USLU with WATANABE et al will not lead to the presently claimed invention since neither of these references discloses compositions which contain microparticles of alendronate.

The Examiner has also cited BLACK *et al.* which discloses a combination formulation for the use in bone loss therapy and which comprises a biphosphonate as a second compound. BLACK *et al.* does not intend to protect a formulation containing alendronate and sweetening agents in a sachet formulation although sachet formulation and use of sweetening agents is mentioned in the description part. Sachet formulation is listed with all other formulations (see paragraph [0110]) in a "broadcast disclosure" and the optional use of the sweetening agents is disclosed in the phrase "The formulations may also include …, sweetening agents, …" (see paragraph [0111]) The presence of sweetening agents in a sachet formulation for improving flavor and taste is not surprising or inventive anyways. Applicants do not claim the use of sweetening agents in the composition as basis for the invention, but it is just a feature of the invention. Therefore, again BLACK *et al.* can not be a motivation for Applicants to use a sachet formulation in the compositions as claimed. As mentioned before, the motivation for Applicants to use a sachet formulation is to prevent the possible destruction of the coated alendronate microparticles. And once again there is no disclosure in any of the cited references of coated microparticles of alendronate with a protective polymer insoluble at the salivary pH of 6 to 7.5, but soluble at the lower gastric pH for any purpose at all, and

especially no suggestion to coat the microparticles of alendronate with the polymers for the purpose of preventing esophageal reflux.

And finally TRITTHART *et al.* is cited by the Examiner for its disclosure of an effervescent oral dosage form with an alkali-sensitive active ingredient and an effervescent base. TRITTHART *et al.* teaches that sachets are useful forms for adapting formulation to be dissolved in water before being taken (see claim 2). Dissolving sachet formulations in water is common general knowledge; the sachet formulations are prepared to dissolve in water. Therefore this mere disclosure of pharmaceutical compositions in the form of a sachet in no way leads to the presently claimed invention which includes microparticles of alendronate coated with a polymer insoluble at the salivary pH of 6 to 7.5, but soluble at a gastric pH of 1 to 4, and which further contains alginic acid or sodium alginate.

In particular Applicants believe that new claim 11 is patentable over the cited combination of references since new claim 11 sharply focuses on the exemplified composition on page 5 of the present application. There is no suggestion in the combination of USLU, WATANABE et al, BLACK et al and TRITTHART *et al* to arrive at the presently claimed invention, for the reasons set forth hereinabove.

Therefore, Applicants do not agree with the Examiner that the presently claimed invention is obvious in view of the combination

of cited references.. Because, "An orally administrable pharmaceutical formulation packaged into a sachet form comprising alendronate microparticles coated with a polymer insoluble at pH 6 - 7.5, but soluble at a gastric pH of 1 to 4, and alginic acid or sodium alginate or admixtures thereof in an amount therapeutically effective to prevent esophageal reflux, heartburn and esophagitis in a patient taking alendronate" is unique, new and inventive and which can not be predicted by just combining the documents listed in the office action. The invention solves a very specific problem arose in the prior art namely preventing esophageal reflux, heartburn and esophagitis in a patient taking alendronate. Also neither the problems needed to be solved nor the percentages of active materials (alendronate and alginate) in the listed patents overlay with the subject of Applicants' invention. Because all these features listed in Applicants' presently claimed invention better serve a patient taking alendronate to prevent esophageal reflux, heartburn and esophagitis, than any of the compositions in the cited references, Applicants alone have found a solution to this significant problem that has been associated with alendronate for many years.

Applicants now give the following direct comments regarding the Examiner's citation of WO 03/043641 as an effective prior art reference in the examination of this application. Applicants do not believe that this reference should not serve as "an inventive step destroying document", in combination with the cited secondary references, namely, WATANABE et al, BLACK et al, and TRITTHART et al, because the document was not published until 30 May 2003 which is after the date that Applicants filed their patent application in Turkey on 18 April 2003, the priority of which the Applicants have claimed and perfected. Since the document was not available to the public at the time that the Applicants even filed their patent application in Turkey, let alone available at the time that the Applicants made their invention in Turkey, how can the reference be a motivating basis for the Applicants to use alginic acid in combination with alendronate, where the alendronate is coated with the polymer?

Applicants believe that all claims now presented are allowable and a response to that effect is earnestly solicited. Applicants enclose payment to obtain a one month extension of the term for response, which may be charged to the credit card of the undersigned attorneys.

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Enclosure: Extension Small Entity (one month)